REMARKS

Applicant notes appreciatively that certain rejections have been withdrawn. The Examiner provides a single rejection:

> Claims 7-12, 15-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,723,120 (Brakenhoff et al) in view of U.S. Patent No. 5,888,511 to Skurkovich *et. al.* and further in view of the '098 patent to Coleman *et. al.*.

Applicant cannot agree and responds below.

The Claims Are Not Obvious

a. The Proper Standards For A 103 Rejection Have Not Been Used

To establish *prima facie* obviousness, the Examiner must point to some motivation or suggestion within the references themselves, or within the knowledge generally available to one of ordinary skill in the art at the time of invention, to combine or modify the references. *See* MPEP §2143.01; *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Merely because the references ***could be*** combined or modified does not render the resultant combination obvious unless the prior art suggested the combination. MPEP §2143.01; *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990).

Applicant submits that the references cannot be considered collectively until the Examiner points to some *evidence* to support combining those references. The purpose behind this requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent decision, articulates this position:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

See In re Rouffet et al., 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). It is readily apparent that the law of *In re Rouffet* requires the Examiner to present soundly reasoned

arguments based upon the substance of the cited references.[1] Moreover, the law does not regard the Examiner as one skilled in the art. *See In re Rijckaert*, 28 USPQ2d 1955 at 1956 (Fed. Cir. 1993)("[T]he examiner's assumptions do not constitute the disclosure of the prior art."); *See id.* at 1957 ("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears."). Indeed, the Federal Circuit has made it clear that "[b]road, conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614 (Fed. Cir. 1999).

Applicant submits that the Examiner has not provided a sound explanation for combining these references as required by the law in *In re Rouffet*. What the Examiner has provided are unsupported and conclusory statements. Moreover, the Examiner proceeds from a flawed understanding of the primary reference, *i.e* the '120 patent.

b. The '120 Patent Does Not Teach The Embodiment Claimed

The Examiner makes the following statement:

> "The '120 patent further discloses that other agents which may be combined with IL-6 receptor antagonists include monoclonal antibodies directed to cytokines involved in the sepsis pathway, such as antibodies directed to IL-6, and antibodies directed to TNF (column 12, lines 44-50). *Thus, the '120 patent discloses methods of treating patients with sepsis with therapeutic compositions comprising anti-TNF and anti-IL-6 antibodies.*"

(*see* Office Action, p. 3, emphasis added). Applicant has looked carefully at column 12, lines 44-50. In fact, Applicant has read the entire paragraph spanning lines 44 to 59. At no point is there a suggestion of combining anti-TNF antibodies with anti-IL-6 antibodies. Rather, this paragraph teaches that "IL-6 receptor antagonists"[2] can be supplemented with i) antibodies to complement, ii) monoclonal antibody to IL-6, iii) monoclonal antibody to TNF, iv) inhibitors of proteins that cleave the mature TNG, or v) "inhibin." Any one of these is used to supplement the "IL-6 receptor antagonist." The paragraph does not teach combinations[3] of

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1 *Accord Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (stating that the examiner must present convincing line of reasoning supporting rejection).

2 This term is defined in the '120 specification so as to include synthetic variants of wild type IL-6.

3 The Examiner must use only what is actually disclosed in the reference. As the court said in *In re Rosenberger*, "[t]his appears to be an extremely strained interpretation of the reference which could be made only by hindsight." *In re Rosenberger*, 386 F.2d 1015, 1018, 156 USPQ 24, 26 (CCPA 1967).

these supplements.[4] Therefore, there is no basis for the Examiner's statement that the '120 patent teaches "compositions comprising anti-TNF and anti-IL-6 antibodies." With respect to TNF, the combination taught is an "IL-6 receptor antagonist" with a monoclonal anti-TNF antibody.

c. There Is No Basis For Changing The Monoclonal Antibodies

The paragraph of the '120 patent spanning lines 44-59 teaches only *monoclonal* antibodies when discussing either antibodies to TNF or antibodies to IL-6.[5] The Examiner has pointed to nothing *within* the '120 patent as a basis for changing these antibodies from monoclonal antibodies to polyclonal antibodies. "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

Since there is apparently nothing in the '120 patent itself suggesting the change from monoclonal antibodies, the Examiner points to the '098 patent disclosure of polyclonal antibodies. However, the Examiner fails to take note that the antibodies of the '098 patent are directed to "the prevention and treatment of mastitis . . . in dairy cattle" (col. 4, lines 30-33). The '098 patent teaches immunization with bacterial antigens (see col. 4, lines 52-62 as well as the single EXAMPLE discussed in columns 7-8). Applicant finds no teaching within the '098 patent to apply IgY technology to generate antibodies to cytokines and to use such antibodies in the context of humans with sepsis.

Finally, Skurkovich *et. al* (the '511 patent) lacks any teaching for the administration of antibodies to TNF-α, IL-6 or gamma IFN, either singly or in any combination, to mammals for the treatment of sepsis. As such, it adds nothing in combination with the other deficient references.

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[4] Moreover, all combinations - whatever they are - are taught to contain an "IL-6 receptor antagonist." Applicant has added Claim 34 (and dependent claims) directed to an embodiment wherein the formulation only contains (as active ingredients) antibodies to TNF and IL-6.

[5] Applicant notes that Claims 15 specifies polyclonal antibodies. Moreover, new claims have been added that are directed to polyclonal antibodies.

CONCLUSION

The Applicant believes that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that these grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 617.252.3353.

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APPENDIX
CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS
PURSUANT TO 37 CFR § 1.121 (c)(3)

7. A method of treatment, comprising:
   a) providing:
      i) a mammal having symptoms of sepsis,
      ii) a therapeutic preparation, comprising anti-TNF-α and anti-IL-6 antibodies; and
      iii) administering said preparation to said mammal wherein said symptoms are reduced.

8. The method of Claim 7, wherein said therapeutic preparation further comprises anti-IFN antibodies.

9. The method of Claim 7, wherein said mammal is a human.

10. The method of Claim 7, wherein said administering is performed intravenously.

11. The method of Claim 7, wherein said administering is performed orally.

12. The method of Claim 7, wherein said administering is performed parenterally.

15. The method of Claim 7, wherein said antibodies are polyclonal antibodies.

16. The method of Claim 15, wherein said polyclonal antibodies are avian antibodies.

17. The method of Claim 16, wherein said avian antibodies are chicken antibodies.

18. The method of Claim 17, wherein said chicken antibodies are derived from chicken eggs.

34. A method of treatment, comprising:

a) providing:

i) a mammal having symptoms of sepsis,

ii) a therapeutic preparation, consisting of anti-TNF-α and anti-IL-6 antibodies, and one or more inactive ingredients; and

iii) administering said preparation to said mammal wherein said symptoms are reduced.

35. The method of Claim 34, wherein said inactive ingredient is bovine serum albumin.

36. The method of Claim 34, wherein said mammal is a human.

37. The method of Claim 34, wherein said administering is performed intravenously.

38. The method of Claim 34, wherein said administering is performed orally.

39. The method of Claim 34, wherein said administering is performed parenterally.

40. The method of Claim 34, wherein said antibodies are polyclonal antibodies.

41. The method of Claim 40, wherein said polyclonal antibodies are avian antibodies.

42. A method of treatment, comprising:

a) providing:

i) a mammal having symptoms of sepsis,

ii) a therapeutic preparation, comprising polyclonal anti-TNF-α and polyclonal anti-IL-6 antibodies; and

iii) administering said preparation to said mammal wherein said symptoms are reduced.

43. The method of Claim 42, wherein said therapeutic preparation further comprises anti-IFN antibodies.

44. The method of Claim 42, wherein said mammal is a human.

45. The method of Claim 42, wherein said administering is performed intravenously.

46. The method of Claim 42, wherein said administering is performed orally.

47. The method of Claim 42, wherein said administering is performed parenterally.

48. The method of Claim 42, wherein said polyclonal antibodies are avian antibodies.